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I am Dr. Jeffrey P. Koplan, Director, Centers for Disease Control and Prevention (CDC). Thank you, Mr. Chairman and members of the Subcommittee, for your invitation to testify today on the emerging national and global problem of antimicrobial resistance and the response by CDC.

Antimicrobial Resistance as a Public Health Issue

In March 1942, a 33-year-old woman was hospitalized for a month with a life-threatening streptococcal infection at a New Haven, Connecticut, hospital. She was delirious, and her temperature reached almost 107 F. Treatments with sulfa drugs, blood transfusions, and surgery had no effect. As a last resort, her doctors injected her with a tiny amount of an obscure experimental drug called penicillin. Her hospital chart, now at the Smithsonian Institution, indicates a sharp overnight drop in temperature; by the next day she was no longer delirious. That woman was the first U.S. civilian whose life was saved by penicillin, and she died last year at the age of 90.

The typical medical ward of a large city hospital was very different in the 1930s than it is today. Today's wards are filled with patients with cancer, heart disease, or the complications of diabetes or high blood pressure. In contrast, the wards of the pre-antimicrobial era were populated by patients with pneumonia, meningitis, sepsis, typhoid fever, diphtheria, syphilis, tuberculosis, and rheumatic fever. There were few effective therapies for most of these conditions. Many of the patients were young, and most would die of the disease or its complications. But within a few years, many of these bacterial infections, and particularly their complications, rapidly faded to become memories of the pre-antimicrobial era.

Unfortunately, the emergence of drug resistance threatens to reverse the progress prompted by the discovery of penicillin and other miracle drugs that have been developed over the last 50 years. Even with these miracle drugs, infectious diseases are a leading cause of death worldwide and the third leading overall cause of death in the United States. Antimicrobial resistance contributes to the burden of infectious diseases domestically and globally including bacterial, fungal, parasitic and viral diseases. Antimicrobial resistance already affects virtually all of the pathogens we have previously considered to be easily treatable. Here in the 21st century, drug options for the treatment of common infections are becoming increasingly limited, and reliance on more expensive options contributes to escalating health care costs. A 1995 Office of Technology Assessment report estimated that the emergence of antimicrobial resistance among six common bacteria in hospitals adds approximately $661 million per year in hospital charges, and this estimate does not include indirect costs. Many other scientific, policy, and government organizations have called attention to this issue, including, in the United States, the American Society for Microbiology, the Infectious Diseases Society of America, the Institute of Medicine, and the General Accounting Office. International organizations that have expressed concern about this issue include the World Health Organization, the European Union, the United Kingdom House of Lords, and Health Canada.

Antimicrobial resistance is a complex and multifaceted public health issue. The use of antimicrobials in agriculture can lead to the development of resistant strains of pathogens that can spread to humans through the food supply or through contact with infected animals. International travel and trade increases the likelihood that drug-resistant pathogens from distant corners of the

world can appear in the United States. For example, malaria is frequently brought into our country by U.S. travelers, and is being transmitted domestically at an increasing rate. Because drug-resistant strains of malaria now predominate across the globe, they present a growing problem here. This complexity highlights the importance of a coordinated, overarching multidisciplinary public health approach that involves physicians, epidemiologists, laboratory and behavioral scientists, veterinarians, and health educators. We are all striving to make antimicrobial resistance a manageable problem that does not compromise the availability of safe and effective drugs to treat infectious diseases.

Drug resistance is one of the target areas in CDC's plan, *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century*. Public health priorities in the plan are organized under four broad, interdependent goals, each of which can be applied to antimicrobial resistance: improving surveillance and response capacity, addressing applied research priorities, repairing the Nation's public health infrastructure and training programs, and strengthening prevention and control programs. Copies of CDC's plan have been provided to the Subcommittee.

Surveillance and Response

Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of health data that results in public health action. These data are used to detect outbreaks, characterize disease transmission patterns, evaluate prevention and control programs, and project future health care needs. In the case of drug resistance, surveillance data available in a timely manner at national, state, and local levels are needed to help clinicians know which antimicrobials to prescribe, help researchers focus their efforts to develop new drugs and vaccines, and help mount campaigns to improve antimicrobial use and infection control practices.

With the exception of drug-resistant tuberculosis, which is reportable in all 50 states, many states do not require reporting of other drug-resistant infections. In those states where drug-resistant infections are reportable, the extent and type of reporting varies. To obtain more systematic information, CDC, in collaboration with state and local health departments and other partners, conducts limited surveillance in some areas to monitor resistance for several important pathogens. For example, surveillance for resistance among invasive pneumococcal infections is conducted through the nine state health departments involved in CDC's Emerging Infections Program cooperative agreements. Surveillance is also conducted in 300 hospitals for healthcare-acquired infections, in 15 states in collaboration with the Food and Drug Administration (FDA) and the Department of Agriculture for foodborne infections, and in 25 clinics for gonoccocal infections. Other projects monitor drug resistance in *Helicobacter pylori*, typhoid fever, HIV, and malaria, but only in a handful of sites. In many communities, the rates of drug resistance for common, serious infections are based on limited and potentially unreliable data or are simply unknown. Existing systems are not well-coordinated.

For many infections, resistance rates vary widely among communities and among hospitals within communities. As one example, data show that the penicillin resistance of *Streptococcus pneumoniae* can vary considerably by location: 15 percent of strains in parts of Maryland are

resistant to penicillin, whereas in five Tennessee counties, 38 percent are resistant. In Connecticut the frequency of resistance varies from zero to 39 percent among hospitals. These data highlight the need for such information at all levels–local, state, and federal–in order to guide clinical decisions and target interventions.

None of these surveillance systems is operational in all 50 states, in all hospitals, or covers all organisms for which antimicrobial resistance is a problem. Coordinated national antimicrobial resistance surveillance is needed to monitor antimicrobial resistance in microorganisms that pose a threat to public health. Core capacities at state and local levels need to be defined. A system to monitor patterns of antimicrobial drug use needs to be developed and implemented. This information is essential to interpret trends and variations in rates of antimicrobial resistance, improve our understanding of the relationship between drug use and resistance, and help identify interventions to prevent and control antimicrobial resistance.

Applied Research

Applied research needs include developing new drugs and vaccines; identifying molecular mechanisms of drug resistance and risk factors associated with its development and spread; developing new and improved rapid diagnostic laboratory tests; and, in collaboration with other agencies and private industry, assessing the role of new vaccines and orphan drugs in preventing and controlling the spread of resistant infections. These and related research needs will require collaboration with other agencies and private industry.

CDC has entered into a promising research collaboration with a consortium formed by the University of Mississippi, Tulane University, and Xavier University in New Orleans to develop and test new antimalarial drugs. This work builds on the complementary strengths of the universities. It focuses on the use of computer-assisted drug design and natural products in the development and testing of promising new medicines.

We also need to develop, implement, and evaluate preventive interventions, including infection control strategies, such as those in hospitals, day care centers, long-term care and home health care settings; improve drug-prescribing practices of health care providers; and the use of vaccines to prevent drug-resistant infections. For example, a new conjugate vaccine for children against *Streptococcus pneumoniae*, the leading cause of pneumonia, meningitis, and ear infections, was licensed for use in February 2000. CDC is evaluating the impact of introduction of this vaccine on drug-resistant pneumococcal infections in children. Research is also necessary to evaluate the impact of drug resistance, including clinical outcomes and economic costs of treating resistant infections. Without these kinds of studies, it is extremely difficult to develop and recommend prevention and control measures to institutions and communities.

Infrastructure and Training

CDC's ongoing effort to rebuild the U.S. public health infrastructure to address infectious diseases is critical in improving the capacity of health departments, health care delivery organizations, and clinical and public health laboratories to detect and report drug-resistant

infections and to implement prevention and control strategies. Part of this effort includes enhancing capacity to respond to outbreaks and training public health professionals to be able to respond to emerging threats now and in the future. Antimicrobial resistance is a constantly changing challenge requiring that laboratory testing methods be kept up-to-date. For example, a 1998 survey was conducted among laboratories that routinely collaborate with CDC. Only 18 percent were actively using appropriate methods to detect emerging resistance in *Staphylococcus aureus*, and only 32 percent were using appropriate methods to find resistance in organisms that typically cause infections in intensive care units. Thus for two important groups of hospital-acquired infections, less than one-third of laboratories were performing proficiently.

We need to ensure that laboratories remain up-to-date with training and that whenever a doctor sends a specimen for culture to a laboratory, the correct test will be done to detect drug resistant infections, the test result will be interpreted correctly and reported to the doctor in a way that helps to select the appropriate drugs, and, if appropriate, reported to a surveillance system. CDC's Epidemiology and Laboratory Capacity agreements to health departments in 43 states and localities currently help support these types of efforts. In addition, the Emerging Infectious Diseases Laboratory Fellowship Program is a partnership between CDC and the Association of Public Health Laboratories designed to prepare laboratory scientists for careers in public health.

Prevention and Control

Perhaps the most daunting challenge is to develop a coordinated program to prevent the spread of antimicrobial resistance by translating information gleaned from surveillance and research into practical public health prevention and control measures. We can all relate to the parent awake at night with a sick child. All that person wants is for his or her child to feel better. For too long, that has often meant requesting an antibiotic from the child's doctor. Although antibiotics work for bacterial infections, we now know that they are not effective for many conditions for which they have been prescribed including fluid accumulation in the middle ear, colds, and bronchitis.

CDC has conducted focus groups with parents and physicians to better understand the factors behind inappropriate antibiotic use. We learned many things from these conversations. For example, parents told us they need an antibiotic in order for their children to return to daycare. This led us to develop a daycare letter that parents can use to get around this ill-conceived policy. Physicians told us that they do not typically have enough time to educate a patient about the problem of antimicrobial resistance and the reasons why antibiotics do not work for viral infections. This reinforced our belief that we must move forward on a nationwide public information campaign.

A key component of CDC's plan to address antimicrobial resistance is promoting appropriate antimicrobial drug use. CDC is developing a national campaign to improve physician prescribing practices and to educate parents and patients about the proper use of antibiotics. By promoting better communication between the public and the medical community, we are attempting to change the entire culture around which antibiotics are prescribed. We are working towards a day when a patient or parent sees his or her health care provider and rather than requesting an

antibiotic, asks for the best treatment available. Where antibiotic use is appropriate, CDC promotes methods to increase adherence to and completion of treatment. For instance, CDC uses directly observed therapy, short-course (DOTS), to ensure patient compliance with tuberculosis treatment. Use of DOTS has increased the proportion of patients completing therapy, lowering the incidence of multidrug-resistant tuberculosis. CDC and FDA have also worked with the American Veterinary Medical Association in its activities to develop prudent-use guidelines for therapeutic veterinary uses of antimicrobials, and CDC strongly supports the new framework articulated by FDA to consider the impact on human drug resistance as part of the approval process for antimicrobials used in food animal production.

In cooperation with professional societies, CDC has developed educational materials for physicians and parents, including a "prescription pad" for physicians to provide patients written instructions for treating symptoms of viral illnesses, for which antibiotics would be inappropriate. In collaboration with AAP and the American Society for Microbiology, CDC has also developed a brochure for parents, *Your Child and Antibiotics*, explaining why antibiotics should not be given for most colds, coughs, sore throats, and runny noses. These materials have been distributed widely and are available on the CDC website. Interventions using these materials and behavioral strategies, such as physician-peer discussions, have proved successful in several locations, including managed care settings in Boston and Seattle, rural communities in northern Wisconsin, Alaska Native villages, and on a county-wide basis in Knoxville, Tennessee. Preliminary data suggest that these approaches are effective. For example, in certain rural Alaskan villages, an education intervention for the public and health care providers successfully reduced antibiotic prescribing by 31 percent. No change was seen in communities not receiving the intervention. Although work is ongoing to measure the impact of reduced antibiotic prescriptions on drug-resistance in the community, these data hold promise that we do have the ability to make a difference.

Appropriate drug-use policies should be implemented through a public health education campaign that promotes appropriate antimicrobial drug use as a national health priority. Improved diagnostic practices should be promoted, including the use of rapid diagnostic methods to guide drug prescribing. Reduced infection transmission should be addressed through campaigns that promote vaccination and hygienic practices such as hand washing and safe food handling. Infection control in health care settings should be enhanced by developing new interventions based on rapid diagnosis, improved understanding of the factors that promote cross-infection, and modified medical devices or procedures that reduce the risk of infection.

Comprehensive, multi-faceted programs involving a wide variety of non-federal partners and the public are required to prevent and control antimicrobial resistance. We need to support demonstration projects that use multiple interventions to prevent and control antimicrobial resistance. We need to encourage the incorporation of effective programs into routine practice

by implementing model programs in federal health-care systems and promoting the inclusion of antimicrobial resistance prevention and control activities as part of quality assurance and accreditation standards for health care delivery nationwide.

Examples of Successes in Preventing Antimicrobial Resistance

Although there has been much discussion of how the problem of antimicrobial resistance is increasing, it is also important to note some successes that provide models for future programs. Public health officials in Iowa, in partnership with physicians and health departments in Nebraska and South Dakota, the Indian Health Service, and CDC, recently succeeded in halting an increase in acquisition of vancomycin-resistant enterococci (VRE) among hospitalized patients and residents of long-term care facilities in the tri-state Siouxland region surrounding Sioux City, Iowa.

VRE is a highly resistant organism that is transmitted in health-care settings. Some patients carry the organism without experiencing symptoms, but others develop infections that may be life-threatening. After a rapid increase in VRE was reported in early 1997, a task force was formed by the Siouxland district health department, consisting of local physicians, infection control practitioners, and public health officials.

The VRE task force formulated several interventions, including performing screening cultures on admitted patients, implementing strict infection control policies based on CDC guidelines, and educating health care workers about the epidemiology of VRE and prudent use of antibiotics, especially vancomycin. This strategy was effective. Over a two year period, the overall prevalence of VRE at all the healthcare facilities decreased from 2.5 to 0.5 percent. There was an elimination of VRE from all the hospitals and a significant reduction in VRE at the long-term care facilities. The key to success was the partnership between public health and clinical medicine so that when surveillance data indicated an emerging problem, science-based prevention and control measures could be implemented rapidly to prevent the spread of a serious drug-resistant infection in this community.

Other countries are grappling with problems of drug resistance as well, and we can learn important lessons from their experiences. In the early 1990s, Finland noted a dramatic increase in resistance of Group A streptococci to the antimicrobial drug erythromycin. Use of erythromycin had tripled and drug-resistance rates correlated with the level of use in local areas. A program of public and physician awareness combined with changes in recommendations for prescribing resulted in reduced erythromycin prescribing for minor outpatient infections and a steady decrease in erythromycin resistance rates among Group A streptococci. It was uncertain if this success could be replicated in a country like the United States with a more heterogeneous population and health care system, but preliminary findings from intervention studies sponsored by CDC and others are encouraging.

Another success relies on modern information technology, which can facilitate rapid collection, analysis, and feedback of information to clinicians. A pioneering program of computer-assisted

decision support developed at LDS Hospital in Salt Lake City offers antibiotic recommendations to clinicians based upon computerized assessment of the patient's medical record and surveillance data on drug resistance in the health care system. This program was developed with input from local physicians, who view it as a valuable resource. The program is associated with decreased inappropriate antibiotic use, reduced frequency of adverse drug reactions, reduced patient care costs, and a stable rate of drug resistance.

Collaboration to Address Antimicrobial Resistance

Combating antimicrobial resistance will require federal leadership and close collaboration among public and private sector partners. Federal agencies need to work together with partners in clinical medicine, laboratory and behavioral science, state and local public health agencies, industry, and the public. International cooperation is also critical. Together, we need to develop public health goals and objectives, along with time frames for implementation.

Beginning in June 1999, CDC, FDA, and the National Institutes of Health joined with seven other federal agencies and departments to form an Interagency Task Force on Antimicrobial Resistance to develop *A Public Health Action Plan to Combat Antimicrobial Resistance*. In addition to the three lead agencies, the Task Force includes members from the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, and other agencies of the Department of Health and Human Services, including the Agency for Healthcare Research and Quality, the Health Care Financing Administration, and the Health Resources and Services Administration. The *Action Plan* provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. It reflects a broad-based consensus of federal agencies, which was reached with input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. Implementation of this plan will require close collaboration with all of these partners, which is a major goal of the process. This summer, the draft of the *Action Plan* was provided for public comment. The Interagency Task Force has recently completed reviewing comments received through this process and is now modifying the *Action Plan* for final publication. This draft plan identifies 11 top priority action items, and overall it has 87 specific action items addressing the important areas of surveillance, prevention and control, research and product development.

The *Action Plan* includes a summary and a list of issues, goals, and action items and specifies "coordinator" and "collaborator" agencies or departments, and timelines for each. CDC's primary role is in the areas of surveillance and prevention and control, addressing the needs I have detailed already in this testimony. The Interagency Task Force will facilitate coordination among agencies and monitor implementation of the *Action Plan*. The Task Force plans to produce periodic reports detailing how the plan is being implemented, solicit comments from the public, and update the Plan as new information and issues arise. Copies of this draft plan have been distributed to the Subcommittee members. This document is Part I of the Action Plan, focusing on domestic issues. Since resistance transcends national borders and requires a global approach to its prevention and

control, Part II of the plan, to be developed subsequently, will identify actions that address international issues.

Conclusions

In conclusion, recent increases in antimicrobial resistance are cause for serious concern but not pessimism. The rapid spread of resistance demands an immediate and aggressive response domestically and globally. Preliminary data suggest that antibiotic prescribing practices can be improved. By forming effective partnerships involving clinicians, researchers, public health officials, and patients, we can prolong the effectiveness of currently available antimicrobial drugs; accelerate the development of needed new tools, including rapid diagnostic tests, new antimicrobial agents, and new or improved vaccines; and reduce the threat of antimicrobial resistance for patients today and in future generations.

Thank you very much for your attention. I will be happy to answer any questions you may have.